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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SRIVASTAVA, KAILASH C	

ART UNIT	PAPER NUMBER
1657	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,415	WEISGRABER ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10.17.03,1.8.04&10.5.06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' responsive communication filed 02 August 2006 in response to Office Action mailed 05 July 2006 is acknowledged and entered.

2. The Art Unit Location for your application under prosecution at the United States Patent and Trademark Office (i.e., USPTO) has been changed to Art Unit 1657. To aid in correlating any papers for this application (i.e., 10/626,415), all further correspondence regarding this application should be directed to Examiner Kailash C. Srivastava in Art Unit 1657.

Claim Status

3. Claims 5 and 12 have been amended.

4. Claims 1-21 are pending.

Restriction/Election

5. Applicants' election with traverse of Group I, Claims 1-4 and 21 filed 02 August 2006 to election requirement in Office Action mailed 05 July 2006 is acknowledged and entered. Applicants' traversal is on the grounds that examining all the claims in this application together will not cause a serious burden to the Examiner, and according to MPEP §803, "the Examiner must examine the entire application on the merits, even though the entire application includes claims to independent or distinct inventions".

Applicants' arguments have been carefully considered, but are not found persuasive because of the reasons of record on pages 3-6, items 8-11 in Office Action mailed 05 July 2006 and for additional reasons discussed below.

The search for each of the distinct inventions of Groups I-IV is not co-extensive particularly with regard to the literature search because each one of those groups is drawn to an invention having steps that distinguish each one of the groups from the other. Thus, each group requires a different search strategy with different key words for each of the inventive groups cited in Office Action mailed 05 July 2006. In addition, the burden lies not only in the search of U.S. patents, burden also lies in the search for non-patent scientific and commercial literature,

foreign patents, and examination of the claim language and specification for compliance with the statutes concerning new matter, distinctness and scope of enablement. Clearly, different searches and issues are involved with each group. Moreover, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the condition for patentability is different in each case. For these reasons, the restriction requirement is still deemed proper, is adhered to and is made FINAL.

Accordingly, Claims 5-20 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR §1.142(b) and MPEP § 821.03.

6. Claims 1-4 and 21 are examined on merits.

Priority

7. Applicants' claim for domestic priority under 35 U.S.C. 119(e) to 60/402,470 filed 09 August 2002 is acknowledged.

Claim Rejections - 35 U.S.C. §112

8. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

9. Claims 1-4 and 21 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession; at the time the invention was made, of the specific subject matter claimed. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude, "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565,

1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or sub-combinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP §2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP §2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what does not constitute a representative number of species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are:(1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." (MPEP §2163).

In the instant case, the claims are drawn to the genus of an isolated apoE stable folding intermediate, wherein said intermediate is an apoE4 stable folding intermediate comprising an N-terminal fragment of about 22kDa and is at least about 80% pure. In the specification, however, only a full-length apoE and one 22kDa N-terminal fragment are disclosed. The claimed invention is assessed as follows with regard to the written description factors listed *supra*.

(a) Level of skill and knowledge in the art:

At least a Bachelor Degree in Biochemistry, Chemistry, Microbiology or Molecular biology.

(b) Partial structure:

The specification citing GeneBank Accession Numbers states that the amino acid sequences (i.e., partial structure) of the mature and intermediate apoE stable folding polypeptides are known in the art. However, there is no description as to which sequence represents which intermediate, nor is there any guidance to determine the sequence of a given stable folding intermediate.

(c) Physical and/or chemical properties:

The physical and chemical properties of the claimed apoE stable folding intermediate are described only in terms of the molecular weight of a given stable folding intermediate and further describing the art-known instrumentation to distinguish one stable intermediate from another. However, except for the molarity of urea at which one stable folding apoE isomorph may be found in abundance as compared to other, there is no guidance to distinguish one stable intermediate from other because all the folding intermediates have same molecular weight (i.e., 22kDa; See Specification Page 9, Line 3 to Page 11, Line 4).

(d) Functional characteristics:

The specification only provides that reduction in the activity/levels of "apoE stable folding intermediates are useful in treating cardiovascular disorders (e.g., high serum lipid levels) or apoE4-associated neurological disorders (Page 27, Lines 22-27).

(e) Method of making the claimed invention:

Despite providing a limited guidance to all the above four written description factors and also the methods to purify certain apoE stable intermediates from a protein, the specification as currently presented does not give any guidance or indication to a method to make the claimed isolated apoE4 stable folding intermediate. It is also not clear how a folding intermediate apoE will be stable.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Claim1 is a broadly generic to all possible apoE stable folding intermediates encompassed by the claims. The possible variations are enormous to any class of polypeptides. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the claimed apoE stable folding intermediates beyond those cursorily mentioned at Page 27, Lines 22-27 of the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of isolating the claimed apoE stable folding intermediates or claimed apoE4 stable folding intermediate.

While having written description of apoE stable folding intermediates identified in the specification tables and/or examples, the specification is devoid of a description to isolate apoE4 stable folding intermediate, or any particular apoE stable folding intermediate that qualify for the functional characteristics claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and

does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

10. Claims 1-4 and 21 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

From the record of the present written disclosure, the specification, while enabling for a full-length apoE stable folding intermediate does not reasonably provide enablement for a composition comprising any apoE intermediate (e.g., apoE2, apoE3) or the 22 kDa N-terminal fragment thereof, or an isolated apoE4 stable folding intermediate, because as illustrated above, there is no description to prepare a composition comprising an isolated apoE4 stable folding intermediate. Furthermore, from the record of the present disclosure Claims 2-4 and 21 are also not enabling because absent the amino acid sequence and detailed structure for said N-terminal fragment of apoE4, there is no disclosure describing how said fragment would stably fold because the 22 kDa size and disclosed purity for said apoE4 stable folding intermediate or N-terminal fragment thereof do not provide enough information for one of ordinary skill to practice the claimed invention.

A person having ordinary skill would not be able to practice the invention because undue experimentation will be required to obtain a composition comprising claimed apoE4 stable folding intermediate or N-terminal fraction thereof cited *supra* due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated below.

(a) Quantity of Necessary Experimentation

Since the specification does not provide any information on how the isolated apoE4 was obtained or which fragment would be useful in the claimed invention and gives the information that a mixture of apoE3 and apoE4 were obtained (See specification page 9, Line 3 to Page 11,

Line 4) an artisan of ordinary skill would have to make a number of permutations and combinations comprising deleting 1, 2 or 3 or more amino acids from the two species disclosed in the specification to obtain isolated apoE4 from a given mixture of peptides and further test each and every fragment to determine the structure-function relationships of each fragment to obtain one having the folding activity of instantly claimed apoE4.

(b) Limited Amount of Guidance

The specification as currently presented does not provide a clear-cut guidance for any thing but the two disclosed intermediates fragments and therefore, no guidance to isolate an apoE4 stable folding intermediate from a mixture of peptides despite art-known techniques to hydrolyze an apoE.

(c) Limited Number of Working Examples in the Specification

The specification does not provide any specific example to isolate an apoE4 or to make a composition comprising an isolated apoE4.

(d) Nature of the Invention

The invention is particularly drawn to a composition comprising an isolated apoE4 stable folding intermediate comprising an N-terminal fragment of apoE4 having 22kDa and about 80% purity without describing how to isolate an apoE4 stable folding intermediate.

(e) State of the Prior Art

From the description of the prior art given in the specification, ApoE is a single gene product, a protein of 34 kDa having at least three isomers and two domains: an amino and a carboxy-terminal domain, wherein each domain has an associated functionality and there is a domain interaction (Page 1, Lines 16-23).

(f) Relative Skill Level of those in the Art

At least a Bachelor Degree in Biochemistry, Chemistry, Microbiology or Molecular biology.

(g) Predictability or Unpredictability in the Art

In the instant case, since only two species arre disclosed, it can not be predicted that any other fragment would have the required properties/function or activity of the claimed material, because unless supported with illustrative experimental evidence, biological responses are unpredictable. Thus, information obtained under one set of detrimental parameters may not be extrapolated for another set of parameters/environmental or specific conditions.

(h) Breadth of the Claims

At least Claims 1 and 21 are broad as they are drawn to any apoE stable folding intermediate. The purity of "at least about 80%" for said apoE stable folding intermediate as currently presented denotes any purity range that includes 80%.

11. Claims 1-4 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with those claims.

The claimed invention is drawn to a composition comprising an isolated apoE stable folding intermediate, wherein said apoE stable folding intermediate is an apoE4 stable folding intermediate comprising an N-terminal fragment of about 22kDa and is at least about 80% pure.

From the record of the present written disclosure, the specification, while enabling to prepare a composition comprising two species or isomorphs of apoE stable folding intermediates, does not clearly describes a composition comprising any isolated apoE4 folding intermediate. Thus, in the absence of demonstrated evidence of record that said composition comprising "an isolated apoE4 stable folding intermediate indeed exists or can be prepared according to the specification of the current application, said specification does not enable an artisan of skill to practice the claimed invention commensurate in scope with said claims.

A person having ordinary skill would not be able to practice the invention because undue experimentation will be required to obtain a composition comprising claimed apoE4 stable folding intermediate or N-terminal fraction thereof cited supra due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples

in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated above.

12. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

13. Claims 1-4 and 21 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Phrase, "isolated apoE stable folding intermediate" renders Claim 1 unclear, vague and therefore indefinite, because it is not clear how without knowing the length or amino acid composition or amino acid sequence for said intermediate, said intermediate apoE will stably fold and what are the conditions under which said intermediate will do so.

- Claims 2-4 are rendered unclear, vague and indefinite because there is no mention of the amino acid composition or amino acid length comprising said apoE4 stable folding intermediate is not defined. Appropriate parameters/properties for said apoE4 stable folding intermediate are required to clearly appraise said apoE stable folding intermediate.

All other claims depend directly from the rejected claims and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

Claim Rejections – 35 U.S.C. § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-4 and 21 are rejected under 35 U.S.C. §102(b) as anticipated by Morrow et al. (Biochemistry, 2000, Volume 39, Pages 11657-11666).

Claims recite a composition comprising an isolated apoE stable folding intermediate, wherein said intermediate is an apoE4 stable folding intermediate comprising an N-terminal fragment of about 22kDa and is at least about 80% pure.

Morrow et al. disclose a composition comprising isolated human apolipoprotein (i.e., apoE) and also to separate not only each of the isomorphs (i.e., aspoE2, apoE3 and apoE4) of said apoE but also the 22kDa fractions of said isomorph (See Figs. 2&3). The 22 kDa fragment comprises residues 1-191. Morrow et al. further establish through guanidine-HCl, urea and thermal denaturation that of the three apoE isomorphs, apoE4 is the least stable (Abstract, Lines 1-11). Morrow et al. also teach that said apoE4 isomorph is also the folding intermediate in apoE (Abstract, Lines 11-12). Note that Morrow et al describe the properties of each one of the isomorphs and especially demonstrate that apoE4 was the least stable folding intermediate. Furthermore, in figure 3 at ~ 2.5M Guanidine-HCl in said reference, a shoulder is present. There is no evidence for any other species at said concentration of Guanidine-HCl. Same is true with 22 kDa species as shown in Figure 2. Hence, prior art reference includes claimed "at least about 80% pure" apoE stable folding intermediate.

Therefore, the reference anticipates claims 1-4 and 21.

Conclusion

16. For aforementioned reasons, no Claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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October 30, 2006

JON WEBER
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